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Body surface area may explain sex differences in findings from the oral glucose tolerance test among subjects with normal glucose tolerance

Samuel Palmu [a,b,*], Susanna Kuneinen [a,b], Hannu Kautiainen [c,d], Johan G. Eriksson [c,e,f,g], Päivi E. Korhonen [a]

[a] *Department of General Practice, Turku University and Turku University Hospital, Turku, Finland*
[b] *Central Satakunta Health Federation of Municipalities, Harjavalta, Finland*
[c] *Folkhälsan Research Center, Helsinki, Finland*
[d] *Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland*
[e] *Department of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[f] *National University Singapore, Yong Loo Lin School of Medicine, Human Potential Translational Research Programme and Department of Obstetrics and Gynecology, SG, Singapore*
[g] *Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR), Singapore*

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Abstract *Background and aims:* Current guidelines on prediabetes and diabetes (T2D) recommend to regularly perform an oral glucose tolerance test (OGTT) on subjects at risk of T2D. However, it is not known why women tend to have relatively higher 2-h post-load plasma (2hPG) glucose concentrations during OGTT than men. The aim of the present study is to investigate if there are sex differences in fasting plasma glucose (FPG) and 2hPG concentrations in relation to body size in apparently healthy non-diabetic subjects with normal glucose tolerance. We hypothesized that sex differences in glucose tolerance are physiological and related to different body surface area (BSA) in men and women.

Methods and results: A 2-h 75 g OGTT was performed on 2010 subjects aged 45–70 years. Their BSA was calculated using the Mosteller formula. Men and women were separately divided into five BSA levels. Within the normal 2hPG range, women had higher mean 2hPG concentrations during the OGTT than men in all BSA levels estimated by sex-standardized BSA (p for linearity < 0.001). BSA adjusted for age, waist circumference, leisure-time physical activity, and smoking, showed an inverse association with 2hPG concentration in both sexes. Mean FPG concentrations were higher in men than in women.

Conclusions: Body size has a negative inverse association with 2hPG concentration in an OGTT even within a physiological plasma glucose range. This may cause underestimation of glucose disorders in individuals with larger BSA and overestimation in individuals with smaller BSA when using an OGTT.

* Corresponding author. 20014, Turun Yliopisto, Finland. Fax: +358 02 9450 5040.
E-mail address: samuel.palmu@utu.fi (S. Palmu).

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Introduction

The global epidemic of obesity is expanding the number of people at risk for type 2 diabetes (T2D), thus increasing the need and use of accurate diagnostic tests [1]. The European and US guidelines recommend to regularly perform an oral glucose tolerance test (OGTT) to subjects at increased risk of T2D [2,3]. This means that in the general population, asymptomatic people with overweight or obesity and one or more additional risk factors for diabetes (e.g. history of gestational diabetes, first-degree family history of T2D) should be screened with an OGTT or a combination of HbA_{1c} and fasting plasma glucose (FPG) [3].

Previous studies using OGTT have shown that impaired fasting glucose (IFG) is more prevalent in men while impaired glucose tolerance (IGT) is more prevalent in women [4]. Of the anthropometric measures, body mass index (BMI) seems to be a better predictor of T2D in men whereas waist circumference (WC) in women [5]. The reasons for these sex differences are not known. Men and women differ by body composition, sex hormones and multiple other factors that control the metabolic homeostasis [4]. It has also been postulated that shorter body height may explain the higher 2-h post-load plasma glucose (2hPG) concentrations in women [6–10]. The determinants of adult height and the association of height and development of T2D and cardiovascular disease (CVD) are just beginning to be understood [11]. When BMI or WC is used as a surrogate measure of body adiposity in clinical practice and in research settings, the effect of body height is diminished or dismissed. Thus, BMI and WC are not applicable nor optimal to measure body size. On the contrary, body surface area (BSA) takes into account both body height and weight as absolute measures and also different body dimensions between men and women. We have previously reported that the smaller the BSA of a person is, the higher is the 2hPG concentration in an OGTT when the effect of central adiposity is adjusted for [12]. Moreover, the inverse relationship of BSA and 2hPG was already present in subjects with normal glucose tolerance indicating a physiological response to the standardized glucose load in the OGTT [12].

The aim of the present study is to investigate if there are sex differences in FPG and 2hPG with relation to body size in apparently healthy non-diabetic subjects. We hypothesized that sex differences in glucose tolerance are related to different BSA levels in men and women.

Methods

Study population

The study subjects were drawn from a population survey, the Harmonica (Harjavalta Risk Monitoring for Cardiovascular Disease) project, which was carried out in southwestern Finland in the rural towns of Harjavalta and Kokemäki in 2005–2007. All home-dwelling inhabitants aged 45–70 years (n = 6013), were mailed an invitation to participate in the project, a validated T2D risk assessment form (The Finnish Diabetes Risk Score questionnaire, FINDRISC, available at https://www.diabetes.fi/english [13]), a cardiovascular risk factor survey, and a measuring tape for WC measurement. The participation rate was 74% (4450/6013).

In the risk factor survey, the participants were asked to report the latest measure of their blood pressure (≥140/90 mmHg regarded as a risk factor), their use of antihypertensive medication, any history of gestational diabetes or hypertension, self-measured waist circumference at the level of the umbilicus (≥80 cm in women or 94 cm in men regarded as a risk factor), and family history (parents/siblings) of coronary heart disease, myocardial infarction or stroke. A FINDRISC score ≥12 in Harjavalta or, for logistics reasons ≥15 in Kokemäki was also regarded as a risk factor (FINDRISC score ≥ 12 indicates that approximately 1 in 6 and ≥ 15 that 1 in 3 will develop T2D within 10 years [13]). Of the 4450 respondents, 3072 (69.0%) had at least one risk factor but no manifested CVD, diabetes or chronic kidney disease. They were invited to further examination performed by a trained study nurse. Valid data of OGTT was available in 2659 study persons.

Laboratory tests were performed after at least 12 h of overnight fasting. OGTT was performed by measuring FPG and 2hPG concentrations after ingestion of a glucose load of 75 g of anhydrous glucose dissolved in water. Glucose concentrations were measured from capillary whole blood samples using the HemoCue Glucose 201+ system (Ängerholm, Sweden). The results were converted from capillary whole blood to capillary plasma glucose values by the analyser. Glucose regulation was classified according to the WHO 1999 criteria [14]. On the basis of OGTT, subjects were classified into normal glucose tolerance if their FPG were <6.1 mmol/l and 2hPG concentrations were <8.9 mmol/l. For the present analysis, only subjects with normal FPG and 2hPG values in OGTT (n = 2010) were included. Plasma total cholesterol, triglycerides and HDL cholesterol were measured enzymatically (Olympus AU604, Japan). LDL cholesterol was calculated by Friedwald's formula [15].

Blood pressure was measured in a sitting position after at least 5 min rest by a study nurse using a calibrated mercury sphygmomanometer. The mean of two readings taken at intervals of 2 min was used in the analyses. Body weight, body height and WC were measured by a study nurse. WC was measured at the level midway between the lowest rib margin and the iliac crest. BMI was calculated as weight (kg) divided by the square of height (m^2). BSA was calculated using the Mosteller formula [weight (kg) x height (cm)/3600]$^{1/2}$ [16]. The relationship with BMI and BSA in the present study population is shown in Fig. 1.

Participants reported education years, leisure-time physical activity (LTPA), smoking status and alcohol use (Alcohol Use Disorder Identification Test, AUDIT [17]) by completing self-administrated questionnaires at the clinic. LTPA was classified as high, moderate or low if ≥ 30 min physical activity at a time was performed six or more, four to five, three or less times a week, respectively.

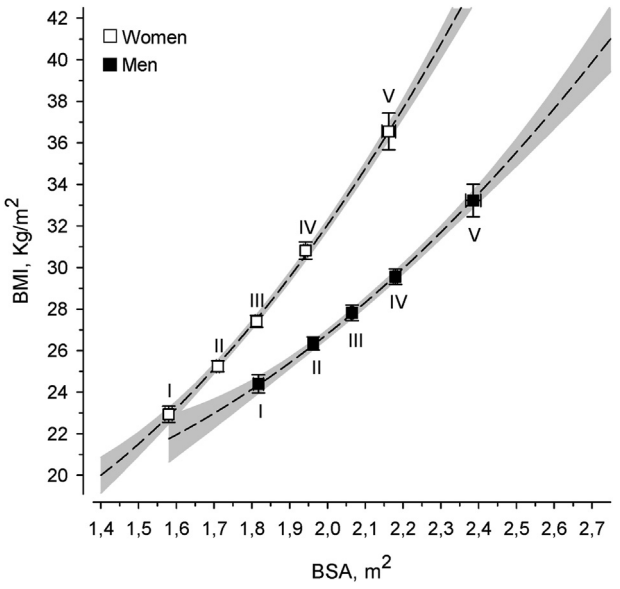

Figure 1 The relationship between body surface area and body mass index levels in men and women. The grey areas represent 95% confidence intervals.

Ethical approval

The ethics committee of Satakunta hospital district reviewed and approved the study protocol and consent forms. All participants provided written informed consent for the project and subsequent medical research.

Statistical analysis

Data were expressed as the mean and standard deviation (SD), or counts and percentages. Men and women were separately divided into five sex specific BSA level categories corresponding 12.5, 25, 25, 25, and 12.5% of the total distribution. Statistical significances for the hypothesis of linearity across gender specific level of body surface area (BSA) were evaluated by using the Cochran–Armitage test for trend and analysis of variance with an appropriate contrast (orthogonal). The main and interactive effects of gender and BSA levels were analyzed by entering gender and BSA and their interaction as independent variables into the models. Age, waist circumference, leisure time physical activity, and smoking were introduced into the models as covariates. Linear regression analyses were used to identify the BSA levels of the glucose tolerance test using crude and adjusted standardized regression coefficients Beta (β). The Beta value is a measure of how strongly each predictor variable influences the criterion (dependent) variable. A possible nonlinear relationship between glucose tolerance test and the sex-specific BSA were assessed by using 4-knot-restricted cubic spline regression. Knot locations were based on Harrell's recommended percentiles [18]. The bootstrap method was used when the theoretical distribution of the test statistics was unknown or in the case of violation of the assumptions (e.g. non-normality). The normality of variables was evaluated graphically and using the Shapiro–Wilk W test. Stata 16.1 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

Results

The study included 2010 participants (841 men, 1169 women) who had normal glucose tolerance. Their mean age was 57 ± 7 years (men) and 58 ± 7 years (women), 58% were women.

Table 1 shows the characteristics of the subjects according to sex and the five BSA categories. In both men and women, increasing BSA level was associated with decreasing HDL cholesterol and increasing triglyceride concentrations as well as higher diastolic BP levels and usage of antihypertensive medication. Subjects with larger BSA were less engaged in LTPA than relatively smaller subjects (p for linearity < 0.001). Male participants with larger BSA were younger (p for linearity < 0.001) and more educated (p for linearity 0.002) than man with smaller BSA. In women only, LDL cholesterol concentration increased with increasing BSA level (p for linearity 0.031).

Although all anthropometric measures rose linearly according to BSA level categories in both sexes (Table 1), at all BMI levels women had lower BSA than men.

In linear regression analysis, BSA showed a negative linear relationship with 2hPG in both men and women independently of age, WC, LTPA, and smoking. The linearity between BSA and FPG was positive in women but disappeared when adjusted for confounding variables (Table 2).

Fig. 2 shows the mean FPG concentrations in relation to sex and BSA levels. The difference between men and women was statistically significant ($p = 0.038$) and was located in the smallest BSA level being 0.18 mmol/l (95% CI: 0.06 to 0.31), $p = 0.004$. There was no linearity between the FPG concentrations and BSA levels ($p = 0.61$), nor an interaction ($p = 0.11$). The continuous BSA spline curve shows that men with BSA below average had higher FPG concentrations compared to women, but no gender difference was observed with larger BSA (Fig. 2).

Women had consistently higher mean 2hPG concentrations than men at all BSA levels ($p < 0.001$). In both sexes, 2hPG concentrations showed a negative linear relationship with BSA levels (p for linearity <0.001) but no interaction ($p = 0.36$). The sex difference in 2hPG concentrations was highest at the largest BSA level, being 0.76 mmol/l (95% CI: 1.15 to 0.37), $p < 0.001$ (Fig. 3).

Discussion

This study demonstrates that within the glucose ranges considered normal, apparently healthy women have higher mean post–challenge glucose concentrations in the OGTT than men in all body size categories estimated by sex-specific BSA. The higher the BSA adjusted for factors related to increased risk for diabetes, the lower is the post–challenge concentration in both sexes. BSA takes into

Table 1 A: Characteristics of male participants according to body surface area level categories.

	I N = 105	II N = 210	III N = 211	IV N = 210	V N = 105	P for linearity
BSA m^2, cm, mean (SD) [range]	1.82 (0.07) [<1.89]	1.96 (0.03) [1.89–2.01]	2.06 (0.03) [2.02–2.11]	2.18 (0.04) [2.12–2.26]	2.39 (0.11) [≥2.27]	
Age, years, mean (SD)	59.0 (6.8)	57.6 (7.0)	58.3 (6.6)	56.3 (6.7)	55.9 (6.4)	<0.001
Education years, mean (SD)	9.6 (2.2)	10.2 (2.5)	9.8 (2.3)	10.9 (2.8)	10.2 (2.3)	0.002
Height, cm, mean (SD)	170 (5)	174 (5)	177 (6)	180 (5)	184 (6)	<0.001
Weigh, kg, mean (SD)	70 (5)	80 (3)	87 (4)	95 (4)	112 (10)	<0.001
Body mass index, kg/m^2, mean (SD)	24.4 (2.3)	26.3 (2.3)	27.8 (2.8)	29.6 (2.8)	33.2 (4.1)	<0.001
Waist circumference, cm, mean (SD)	88.2 (6.8)	94.3 (5.9)	99.4 (6.6)	104.2 (6.5)	114.6 (9.9)	<0.001
Fasting plasma glucose, mmol/l, mean (SD)	5.28 (0.53)	5.22 (0.47)	5.30 (0.48)	5.36 (0.48)	5.28 (0.39)	0.077
2-h post-load plasma glucose, mmol/l, mean (SD)	7.03 (1.46)	6.95 (1.68)	6.83 (1.83)	6.78 (1.70)	6.75 (1.76)	0.12
Total cholesterol, mmol/l, mean (SD)	5.36 (0.93)	5.40 (0.95)	5.24 (0.88)	5.34 (1.03)	5.37 (0.99)	0.78
HDL cholesterol, mmol/l, mean (SD)	1.56 (0.39)	1.52 (0.47)	1.40 (0.36)	1.39 (0.47)	1.21 (0.30)	<0.001
LDL cholesterol, mmol/l, mean (SD)	3.28 (0.80)	3.31 (0.86)	3.25 (0.85)	3.29 (0.94)	3.39 (0.88)	0.52
Triglycerides, mmol/l, mean (SD)	1.19 (0.64)	1.33 (0.67)	1.40 (0.74)	1.56 (0.76)	1.72 (0.73)	<0.001
Blood Pressure, mmHg, mean (SD)						
Systolic	140 (20)	140 (16)	141 (17)	139 (18)	143 (19)	0.34
Diastolic	83 (10)	85 (10)	87 (10)	87 (9)	91 (10)	<0.001
Current smoker, n (%)	28 (27)	37 (18)	45 (22)	40 (19)	14 (13)	0.075
AUDIT score, mean (SD)	6.8 (5.6)	6.6 (5.5)	6.8 (5.2)	6.6 (5.2)	7.0 (5.1)	0.82
Leisure time physical activity, n (%)						<0.001
Low	12 (12)	34 (17)	47 (23)	49 (24)	36 (35)	
Moderate	55 (55)	111 (54)	96 (47)	98 (48)	48 (47)	
High	33 (33)	59 (29)	63 (31)	56 (28)	19 (18)	
Current medication, n (%)						
Statins	7 (7)	22 (10)	34 (16)	25 (12)	10 (10)	0.43
Antihypertensives	21 (20)	48 (23)	71 (34)	68 (32)	46 (44)	<0.001

B: Characteristics of female participants according to body surface area level categories.

	I N = 146	II N = 292	III N = 293	IV N = 291	V N = 147	P for linearity
BSA m^2, cm, mean (SD) [range]	1.58 (0.06) [≤1.64]	1.71 (0.03) [1.65–1.75]	1.81 (0.03) [1.76–1.85]	1.94 (0.05) [1.86–2.03]	2.16 (0.11) [>2.03]	
Age, years, mean (SD)	58.2 (7.6)	58.5 (7.1)	57.8 (6.9)	57.7 (6.8)	57.3 (7.3)	0.11
Education years, mean (SD)	10.9 (2.8)	10.7 (2.9)	10.8 (2.9)	10.6 (2.8)	11.1 (2.9)	0.83
Height, cm, mean (SD)	158 (5)	161 (5)	163 (5)	164 (6)	167 (6)	<0.001
Weight, kg, mean (SD)	57 (4)	65 (3)	73 (3)	83 (5)	101 (11)	<0.001
Body mass index, kg/m^2, mean (SD)	22.9 (2.4)	25.3 (2.3)	27.4 (2.5)	30.8 (3.6)	36.6 (5.5)	<0.001
Waist circumference, cm, mean (SD)	76 (6)	82 (6)	89 (6)	97 (8)	109 (10)	<0.001
Fasting plasma glucose, mmol/l, mean (SD)	5.04 (0.48)	5.16 (0.51)	5.17 (0.49)	5.28 (0.43)	5.29 (0.44)	<0.001
2-h post-load plasma glucose, mmol/l, mean (SD)	6.89 (1.44)	6.85 (1.51)	6.97 (1.43)	6.90 (1.55)	7.30 (1.72)	0.034
Total cholesterol, mmol/l, mean (SD)	5.46 (0.91)	5.57 (0.97)	5.55 (0.93)	5.55 (0.94)	5.54 (0.90)	0.63
HDL cholesterol, mmol/l, mean (SD)	1.84 (0.46)	1.82 (0.41)	1.72 (0.42)	1.61 (0.40)	1.48 (0.34)	<0.001
LDL cholesterol, mmol/l, mean (SD)	3.15 (0.79)	3.26 (0.92)	3.26 (0.85)	3.34 (0.89)	3.34 (0.87)	0.031
Triglycerides, mmol/l, mean (SD)	1.09 (0.65)	1.12 (0.63)	1.28 (0.65)	1.35 (0.59)	1.64 (0.81)	<0.001
Blood Pressure, mmHg, mean (SD)						
Systolic	136 (19)	139 (18)	136 (17)	138 (18)	141 (15)	0.12
Diastolic	80 (10)	81 (9)	82 (9)	84 (9)	86 (9)	<0.001
Current smoker, n (%)	24 (17)	40 (14)	35 (12)	33 (11)	18 (12)	0.16
AUDIT score, mean (SD)	2.8 (3.2)	2.7 (2.8)	2.9 (3.1)	2.9 (2.8)	2.6 (3.4)	0.88
Leisure time physical activity, n (%)						<0.001
Low	16 (11)	23 (8)	32 (11)	46 (16)	34 (24)	
Moderate	61 (42)	149 (52)	148 (52)	143 (51)	80 (56)	
High	67 (47)	115 (40)	104 (37)	94 (33)	28 (20)	
Current medication, n (%)						
Statins	9 (6)	27 (9)	21 (7)	35 (12)	16 (11)	0.071
Antihypertensives	24 (16)	65 (22)	63 (22)	97 (33)	77 (52)	<0.001

Abbreviations: BSA, body surface area; HDL high-density lipoprotein; LDL, low-density lipoprotein; AUDIT, Alcohol Use Disorder Identification Test.
To convert values for glucose to milligrams per decilitre, multiply by 18.016.

account the difference in body size between men and women as opposed to BMI.

The relationship between body size, sex and glucose homeostasis is a complex entity. An increasing number of studies indicate, that sex plays an important part in the metabolic regulation and susceptibility to diabetes [19]. The present study of apparently healthy subjects showed, that men have slightly higher mean FPG than women without

Table 2 Regression models for the relationship between body surface area (BSA) levels and diagnostic variables (FPG and 2hPG) in men and women.

	Fasting plasma glucose (mmol/l)			2-h post-load plasma glucose (mmol/l)		
	Model 1 β[a] (95% CI)	Model 2 β[a] (95% CI)	Model 3 β[a] (95% CI)	Model 1 β[a] (95% CI)	Model 2 β[a] (95% CI)	Model 3 β[a] (95% CI)
Women BSA level						
I	Reference	Reference	Reference	Reference	Reference	Reference
II	0.11 (0.02–0.19)	0.08 (−0.01 to 0.17)	0.08 (−0.01 to 0.17)	−0.01 (−0.10 to 0.07)	−0.09 (−0.17 to −0.00)	−0.09 (−0.18 to −0.01)
III	0.12 (0.03–0.20)	0.06 (−0.03 to 0.16)	0.06 (−0.03 to 0.16)	0.02 (−0.06 to 0.11)	−0.12 (−0.21 to −0.03)	−0.14 (−0.23 to −0.05)
IV	0.22 (0.14–0.30)	0.13 (0.02–0.24)	0.13 (0.02–0.24)	0.00 (−0.08 to 0.09)	−0.23 (−0.33 to −0.12)	−0.24 (−0.35 to −0.13)
V	0.17 (0.10–0.25)	0.07 (−0.04 to 0.18)	0.06 (−0.05 to 0.17)	0.09 (0.01–0.16)	−0.18 (−0.29 to −0.07)	−0.20 (−0.30 to −0.09)
P for linearity	$p < 0.001$	0.15	0.22	0.034	<0.001	<0.001
Men BSA level						
I	Reference	Reference	Reference	Reference	Reference	Reference
II	−0.05 (−0.15 to 0.05)	−0.08 (−0.18 to 0.03)	−0.08 (−0.19 to 0.02)	−0.02 (−0.12 to 0.08)	−0.05 (−0.15 to 0.05)	−0.05 (−0.16 to 0.05)
III	0.02 (−0.08 to 0.12)	−0.03 (−0.14 to 0.08)	−0.05 (−0.16 to 0.07)	−0.05 (−0.15 to 0.05)	−0.15 (−0.25 to −0.04)	−0.14 (−0.25 to −0.03)
IV	0.07 (−0.03 to 0.17)	−0.01 (−0.13 to 0.13)	−0.01 (−0.14 to 0.11)	−0.06 (−0.16 to 0.04)	−0.17 (−0.29 to −0.05)	−0.17 (−0.28 to −0.05)
V	0.00 (−0.09 to 0.09)	−0.09 (−0.22 to 0.04)	−0.10 (−0.23 to 0.03)	−0.05 (−0.14 to 0.04)	−0.21 (−0.32 to −0.09)	−0.22 (−0.34 to −0.10)
P for linearity	0.082	0.70	0.59	0.12	<0.001	<0.001

Model 1: crude.
Model 2: adjusted for age and waist circumference.
Model 3: adjusted for age, waist circumference, leisure time physical activity, and smoking.
[a] The values of the standardized regression coefficients (Beta).

interaction with BSA. This might be related to the fundamental sex differences in the utilization of carbohydrates and lipids as fuel sources [4]. At rest and during the post-absorptive state the female body favors energy storage [5] which might explain why women show lower fasting endogenous glucose production [20], whereas the male body aims at mobilizing energy stores through plasma FFA oxidation [5]. Furthermore, the larger the person, the larger the liver [21] and skeletal muscle mass [22] – thus, probably larger glycogen storage to be mobilized.

Our previous study reported that the OGTT identifies more T2D and IGT in relatively smaller sized individuals [12]. In the present study, we focused on the normoglycemic range and analyzed men and women separately. BSA showed a negative relationship with 2hPG in both sexes, and women had higher mean 2hPG concentrations than men when the effects of age, abdominal obesity, LTPA, and smoking were taken into account. This information is indicative of a physiological phenomenon related to body size. The gut absorption rate of glucose has been found to be slower in women compared with men and to have a negative correlation with height, but not with BMI, in both sexes [20]. Many previous studies have postulated that shorter body height may explain the higher 2hPG concentrations in women [6–10].

Adult height is determined by genetic and environmental factors [23]. Women have on average more adipose tissue and less skeletal muscle mass than men, and women have an increased propensity to gain fat [4]. The relationship between weight and height is not equal between men and women, and BMI is not independent of height, but the correlation is inverse in most populations [24]. With the same BMI, women are likely to have a greater percentage of body fat than men [25]. In epidemiological studies height is rarely taken into account. The importance of proper adjustment for confounding variables such as age, sex and anthropometric measures has recently been addressed also in the 2018 Cochrane review "Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia" [26].

Tura et al. [27] and Kautzky-Willer et al. [28] have assessed metabolism in subjects with normal glucose tolerance with more sophisticated methods than those used in our study. The results showed that females had lower fasting but higher post-load glucose values even after correction for age and BMI [27,28]. Taken together, all these studies imply that sex and body size are important factors to be considered when assessing glucose metabolism with an OGTT.

The main limitation of this study is its cross-sectional setting which prevents to assess causalities. HbA_{1c} was not measured in the present study and relationship with HbA_{1c}, and body size would be a subject of future research. Although the lifestyle-related factors were assessed with self-administrated questionnaires and dietary habits were not gathered, anthropologic measurements were made by

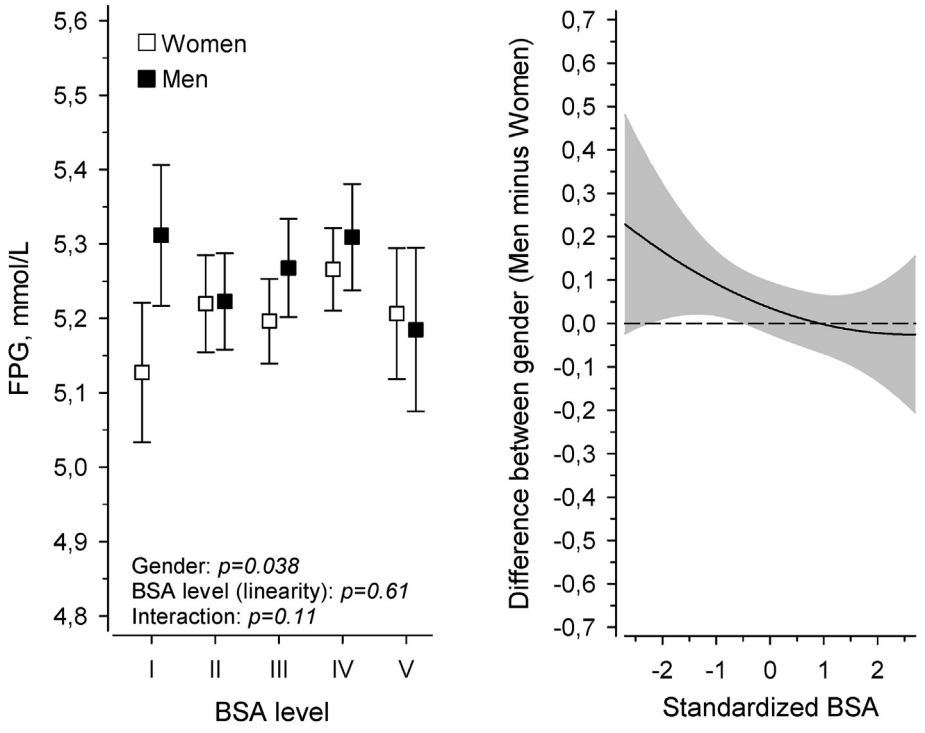

Figure 2 Mean fasting plasma glucose (FPG) by sex-specific body surface area level and sex. Adjusted for age, waist circumference, leisure time physical activity, and smoking. Error bars are for 95% confidence intervals. The difference of continuous FPG between men and women were derived from a 4-knot restricted cubic splines regression model. The grey area represents a 95% confidence interval.

trained medical staff. Another strength of our study is that the study population represents a healthy population at increased risk of diabetes or CVD, to whom OGTT is recommended to be performed, and whose future risk of diabetes is possible to be reduced through interventions. However, our results may not be generalized to persons without any cardiovascular risk factors or persons with glucose disorders.

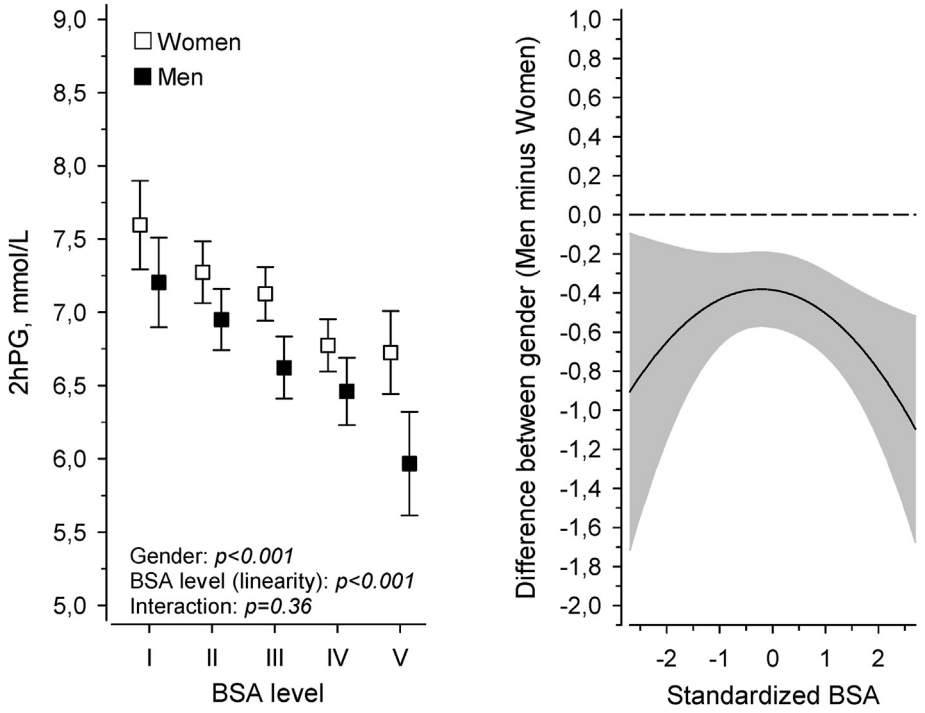

Figure 3 Mean 2-h plasma glucose (2hPG) by gender specific body surface area level and sex. Adjusted for age, waist circumference, leisure time physical activity, and smoking. Error bars are for 95% confidence intervals. The difference of continuous 2hPG between men and women were derived from a 4-knot restricted cubic splines regression model. The grey area represents a 95% confidence interval.

In conclusion, BSA has an inverse relationship with 2hPG concentration in both sexes, and women have higher 2hPG concentrations than men in an OGTT even within the physiological glucose range. This may cause underestimation of glucose disorders with larger BSA and overestimation with smaller BSA when using an OGTT. Albeit our results apply only to people with normal glucose tolerance, we challenge the use of an OGTT as an appropriate diagnostic method to detect glucose disorders.

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Authors' contributions

SP wrote the first draft and participated writing and editing of the report. SK participated writing and editing of the report. KH designed the study and did statistical analysis. JGE participated writing and editing the report and oversaw the preparation of the report as senior author. PEK designed the study, collected data, participated in statistical analysis and writing of the report and oversaw the preparation of the report as senior author. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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